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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.
P O BOX 458
ALAMEDA, CA 94501

EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,082	SWANSON ET AL.	
	Examiner	Art Unit	
	JEANINE A. GOLDBERG	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/8/08; 12/22/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-7,9,10 and 15-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-7, 9-10, 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed September 8, 2008 and December 22, 2008. Currently, claims 1-3, 5-7, 9-10, 15-17 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

3. Any objections and rejections not reiterated below are hereby withdrawn.

a. The 102(a) rejection has been overcome in view of the two 132 Katz type declarations filed on September 8, 2008.

b. The 102(b) rejection over Seaman has been overcome in view of the amendment to the claims to exclude L1.

Election/Restrictions

4. Applicant's election without traverse of Group 1, Claims 1-10 in the paper filed February 19, 2008 is acknowledged.

The requirement is still deemed proper and is therefore made FINAL.

Priority

5. This application is a 371 of PCT/US03/41409, filed December 29, 2003 and claims priority to 60/439,903, filed December 26, 2002.

Drawings

6. The drawings are acceptable.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 6-7, 9-10, 16-17 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The instant claims are directed to a reagent comprising a polynucleotide "corresponding to" a polymorphism in linkage disequilibrium with an allele of DRDR associated with individuals exhibiting ADHD. The claims are not directed to an isolated DNA molecule such that the claims would be directed to statutory subject matter. This rejection may be easily overcome by amending the claims to recite an "isolated polynucleotide" such that it is clear that the "hand of man" is required and the product is nonnaturally occurring.

Response to Arguments

The response traverses the rejection. The response asserts the claims have been amended to add "isolated". This argument has been considered but is not

convincing because Claim 6, for example is not directed to isolated nucleic acids. Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Newly amended and added Claims 1-2, 4-7, 9-10, 15-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Fodor (US Publication 2001/0053519, December 20, 2001).

It is noted that the promoter region, exon 1 and intron 3 polymorphisms are inherently in strong linkage with the DRD4 7R allele.

Fodor teaches analysis using a 10-mer array (Example 2, col. 22). Figures 2-5 show results from the hybridization of a sample of DNA to an array containing all possible 10-mers which was manufactured using photolithography techniques on an array. Within the array there are many polynucleotides that comprise polymorphisms in LD with DRD4 alleles. For example, Fodor inherently teaches an ASO probe of 10 nucleotides that corresponds to the intron 3 polymorphisms which are inherently in LD

with the DRD4 7R allele. Therefore, Fodor teaches a reagent comprising a polynucleotide corresponding to a polymorphism in LD with an allele of DRD4.

Response to Arguments

The response traverses the rejection. The response asserts the claims have been amended to require an isolated polynucleotide but Fodor teaches an array that includes all possible 10-mers on the size of a dime which is not isolated. This argument has been considered but is not convincing because neither the specification nor the art provides any particular limiting definition for "isolated." The nucleic acids provided on Fodor are isolated from cellular material, are isolated from proteins, etc. The nucleic acids on Fodor are also each addressable on separate locations on the array which makes them isolated.

The response asserts that the Fodor array is not configured for SNP genotyping and could not be used for diagnostic purposes. This argument has been reviewed but is deemed not persuasive. Fodor, in his abstract, states the oligonucleotides may be used in medical diagnostics. Furthermore, Fodor specifically states in paragraph 3, 42, for example, as well as Claims 5, 6, 10, 18 specifically are directed to embodiments where the array may be used to identify polymorphisms or biallelic markers. Thus, applicants arguments that Fodor's array is not configured for SNP genotyping does not appear to be supported by the evidence of record.

Thus for the reasons above and those already of record, the rejection is maintained.

9. Newly amended and added Claims 1-2, 6-7, 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Okuyama et al. (Biochemical and Biophysical Research Communications, Vol. 258, pages 292-295, 1999).

Okuyama examined LD of the -521 C>T polymorphism of DRD4 with the exon 3 VNTR polymorphism and found a weak LD. Okuyama further teaches primers which amplify the -521 region of the DRD4 gene. These primers are polynucleotides that correspond to a polymorphism in LD with an allele of DRD4 (limitations of Claims 1, 6). Okuyama further teaches PCR-restriction fragments which comprise the polymorphic allele which is in LD with the DRD4 7R allele. The DRD4 gene is less than 4,000, thus the promoter polymorphism is within 50kB of the 7R allele (limitations of Claims 4-5, 9-10). Therefore, Okuyama teaches a reagent comprising a polynucleotide corresponding to a polymorphism in LD with an allele of DRD4.

Response to Arguments

The response traverses the rejection. The response asserts Okuyama is equivocal as to whether LD actually exists between the -521 C>T polymorphism and the exon 3 VNTR, namely DRD4-7R. This argument has been considered but is not convincing. Applicant is reminded that MPEP 2112.01 teaches "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). 'When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant

has the burden of showing that they are not.'" Here, the art teaches a weak association between -521 C>T polymorphism and teaches oligonucleotides. Applicant does not provide any arguments or evidence that the -521 C>T polymorphism is not in LD with DRD4-7R. The examiner thus, has a sound basis for believing that the products applicant is claiming and the products of Okuyama are the same.

Thus for the reasons above and those already of record, the rejection is maintained.

10. Newly amended and added Claims 1-2, 6-7, 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Seaman et al. (J. of Experimental Zoology, Vol. 288, pages 32-38, 2000).

It is noted that the promoter region, exon 1 and intron 3 polymorphisms are inherently in strong linkage with the DRD4 7R allele.

Seaman teaches primers D4EX1F and D4EX1R that are primer for typing exon 1 12pb polymorphism. These primers correspond to the polymorphism in exon 1 which is in LD with the DRD4 7R allele. These primers are within 50kB of the 7R allele. Thus, the typing primers of Seaman anticipated the claimed invention.

Response to Arguments

The response traverses the rejection. The response asserts Seaman relates to PCR amplification of the 12bp polymorphic tandem repeat, namely L2. The response asserts L2 has been excluded from the claimed subject matter. This argument has been considered but is not convincing because the primers of D4EX1F and D4EX1R

specifically amplify the 13bp polymorphism in exon 1 also which appears to be inherently in LD with DRD4-7R. Thus for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection Necessitated by Amendment

New Matter

11. Claims 4, 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "the polymorphism is within 2.7kb of the DRD4 exon 3 variable number repeat" are included. The amendment proposes that the new claim language is supported in paragraph 60 of the specification. However, the specification does not describe or discuss "polymorphisms within 2.7 kB of the DRD4 exon 3 VNTR" or "polymorphisms within 350 bp of the DRD4 exon 3 VNTR". Instead the specification describes the polymorphisms including two insertion/deletion polymorphisms, one in the promoter region (4.3 kb upstream of the VNTR) and one in exon 1 (2.7 kb upstream of the VNTR; see FIG. 1). In addition, a number of new coding SNPs were uncovered in the exon 3 48 bp VNTR, as well as two previously unreported SNPs in intron 3, 20 nucleotides apart and approximately 350 bp downstream from the center of the VNTR (FIG. 1). This description does not support "the polymorphism is within 2.7kb of the DRD4 exon 3 variable number repeat". The specification merely

teaches one polymorphism is 2.7kB upstream of the 48bp VNTR and SNP polymorphisms are 350 downstream. This is not support for 2.7kB downstream and 350bp upstream. The concept of ""the polymorphism is within 2.7kb of the DRD4 exon 3 variable number repeat" does not appear to be part of the originally filed invention. Therefore, ""the polymorphism is within 2.7kb of the DRD4 exon 3 variable number repeat" constitutes new matter. Applicant is required to cancel the new matter in the reply to this Office Action.

12. Claim 15 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "the polynucleotide is an amplicon" is included. The amendment does not point to any support for the new claim language. A search of the specification does not provide any hits for "amplicon". The concept of "the polynucleotide is an amplicon" does not appear to be part of the originally filed invention. Therefore, "the polynucleotide is an amplicon" constitutes new matter. Applicant is required to cancel the new matter in the reply to this Office Action.

13. Claims 16-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "two or more pairs of isolated oligonucleotides" included. The amendment suggests para 60 supports the new claim language. However, para 60 does not provide any description for two or more pairs of isolated oligonucleotides for amplification of polymorphisms in LD. A search of the specification does not provide any hits for "two or more pairs". The concept of "two or more pairs of isolated oligonucleotides" does not appear to be part of the originally filed invention. Therefore, "two or more pairs of isolated oligonucleotides" constitutes new matter. Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1-2, 4-7, 9-10, 15-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the

'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA…' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. As provided in Example 11 of the Written Description Guidelines, no common structural attributes identify the members of the genus of "a reagent useful for diagnosing ADHD comprising an isolated polynucleotide comprising a polymorphism in LD with DRD4-7R, wherein the polymorphism is other than L1 or L2 polymorphism". The current claims encompass a large genus of nucleic acids which comprise variants in any region of any a marker within a block of linkage disequilibrium surrounding the DRD4 7R allele. The genus includes an enormous number of variants, polymorphisms and mutations for which no written description is provided in the

specification. This large genus is represented in the specification by three named polymorphism for which data is provided, namely the promoter polymorphism (L1/S1), exon 1 (L2/S2) and intron 3 (G-G/A-C) polymorphisms. It is noted that the specification teaches that these polymorphisms are not in complete linkage disequilibrium with the 7R allele.

The instant specification names 3 markers, but these 3 markers are not in 100% linkage disequilibrium. The response asserts the specification, page 11-12, are extremely predictive of that particular allele.

- Promoter polymorphism (L1)- 90.8% of 7R alleles associated with L1 (vs 61.9% of 4R alleles)
- Exon 1 polymorphism (L2)- 93.4% of 7R alleles associated with L2 (vs 86.4% of 4R alleles)
- A-C SNP pair - 97% of 7R alleles were associated with A-C SNP pair. (A-C is associated with the DRD4 4R alleles).

The claims then exclude 2 of the 3 named polymorphisms. Thus, the specification describes a single polymorphism in intron 3 which is within the scope of the claims. This genus encompasses SNPs, deletions, insertions, translocations, microsatellites, for example. The post filing date art analyzes 103 individuals and identifies 70 SNPs/polymorphisms (see Wang et al. Am. J. Hum. Genetics, Vol. 74, pages 931-944, 2004). Table 1, as provided in Wang, provides a few exemplary polymorphisms. Of these polymorphisms, Wang specifically marks a few of the SNPs, deletions and repeats as highly linked to the 7R allele (see Table 1). The instant

specification fails to provide any description of these polymorphisms and the three polymorphisms within the specification are not representative of these polymorphisms. Bhaduri teaches association of DRD4 polymorphisms with ADHD in Indian population. Bhaduri finds the exon 1 12bp duplication and exon 3 48pb VNTR in strong disequilibrium. However, Bhaduri teaches the alleles of 12bp duplication are not associated with ADHD. Thus, there is no description of markers surrounding the DRD4 7R allele which are within linkage disequilibrium and are associated with ADHD.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, a marker within a block of linkage disequilibrium surrounding the DRD4 7R allele alone is insufficient to describe the genus. There is no description of the mutational sites that exist in nature. The general knowledge in the art concerning variants does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures, and in the present state of the art the structure of one does not provide guidance to the structure of others. The common attributes are not described. The polymorphisms shown are not representative of the genus of any a marker in linkage disequilibrium surrounding the DRD4 7R allele because it is not clear which polymorphisms within the gene (coding or non-coding) region of DRD4 nucleic acid would have the same effect. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member

of this genus is not representative of the variants of the genus and is insufficient to support the claim. Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Conclusion

15. No claims allowable over the art.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

/Jeanine Goldberg/
Primary Examiner
March 24, 2009